British Journal of Anaesthesia **104 (1):** 94–7 (2010)
doi:10.1093/bja/aep313 Advance Access publication November 14, 2009

REGIONAL ANAESTHESIA

Electrocardiographic alterations during intravascular application of three different test doses of bupivacaine and epinephrine: experimental study in neonatal pigs

J. Mauch[1 2]*, A. P. N. Kutter[3], C. Madjdpour[2], N. Koepfer[2], A. Frotzler[2], R. Bettschart-Wolfensberger[3] and M. Weiss[2]

[1]Department of Anaesthesia and Perioperative Medicine, Kantonsspital, Aarau, Switzerland. [2]Department of Anaesthesia, University Children's Hospital, Zurich, Switzerland. [3]Section of Anaesthesiology, Equine Department, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

**Corresponding author. E-mail: jacqueline.mauch@ksa.ch*

Background. Origin of electrocardiographic (ECG) alterations during intravascular injection of local anaesthetic solutions is controversial. The aim of this study was to elucidate whether epinephrine, bupivacaine or their combination is responsible for ECG alteration.

Methods. Forty-five piglets were randomized into three groups. After induction of general anaesthesia using sevoflurane and peripheral venous cannulation, the trachea was intubated, the lungs were artificially ventilated, and anaesthesia was maintained by sevoflurane. Under steady state 0.2 ml kg^{-1} and after 10 min 0.4 ml kg^{-1} of one of the following three test solutions was administered i.v.: bupivacaine 0.125% (Group 1), bupivacaine 0.125%+epinephrine 1:200 000 (Group 2), and plain epinephrine 1:200 000 (Group 3). The ECG was analysed for alterations in heart rate and T-elevation.

Results. After injection of 0.2 or 0.4 ml kg^{-1} test solution, an increase in heart rate of at least 10% was found in none of Group 1 and in all of Groups 2 and 3. After application of 0.2 ml kg^{-1} test solution, T-elevation was found in 7% of Group 1 and in 93% of Groups 2 and 3. The injection of 0.4 ml kg^{-1} revealed a T-elevation in 27%, 100%, and 100%, respectively, in Groups 1, 2, and 3.

Conclusions. This animal model demonstrated that increases in heart rate and T-elevation in the ECG during i.v. application of a common test dose (0.2 ml kg^{-1}) of bupivacaine are caused by epinephrine addition. Whether higher doses of bupivacaine alone can cause similar ECG changes or not requires further studies.

Br J Anaesth 2010; **104**: 94–7

Keywords: anaesthetic techniques, regional; complications; heart arrhythmia, tachycardia, bradycardia; heart, conduction; toxicity, local anaesthetics

Accepted for publication: September 25, 2009

The combination of general anaesthesia and regional anaesthesia for intra- and postoperative pain relief in children is a cornerstone in paediatric anaesthesia, and the application of regional anaesthesia during general anaesthesia is a common practice.[1]

However, cerebral signs of local anaesthetic (LA) toxicity due to inadvertent intravascular administration of LAs are blunted by general anaesthesia, muscle paralysis, or both. Objective signs and reliable strategies for detection of inadvertent intravascular administration of LAs have to be used to avoid haemodynamic collapse by unrecognized LA intoxication.

Careful aspiration and passive backflow from the inserted needle or catheter alone before injecting LA are not sensitive enough to detect intravascular placement of the needle or catheter.[2 3] Therefore, the addition of epinephrine to provoke an increase in heart rate has been recommended.[2–4] Monitoring the electrocardiography (ECG) for detection of LA-related changes, particularly an increase in T-wave amplitude, is also recommended for

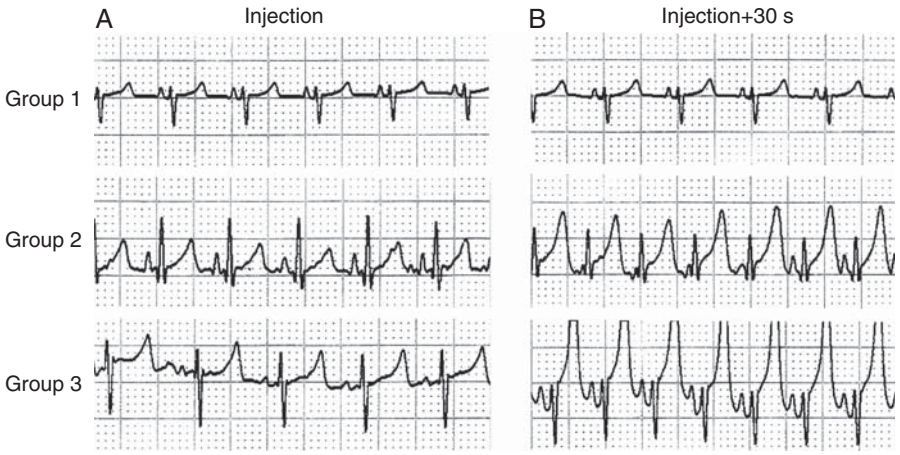

Fig 1 Representative ECG recordings from each group (n=15 piglets per group) investigated: (A) pre-injection; and (B) 30 s after injection of test solution.

the early detection of intravascular injection of LAs,[2 4–6] although the mechanisms responsible for these ECG changes have not been clearly elucidated.[4]

The aim of this study was to determine whether bupivacaine, epinephrine, or their combination is responsible for ECG alterations caused by i.v. administration in a clinically used test dose.

Methods

After obtaining approval from the local Ethics Committee for Animal Experiments, 45 healthy male and female neonatal pigs (up to 6 weeks of age) weighing 4.1–5.9 kg were included. The pigs had free access to food until 1 h before anaesthesia induction. Anaesthesia was induced by the inhalation route using sevoflurane. After establishing a venous access in an auricular vein, the trachea was intubated then the lungs were artificially ventilated using pressure-controlled ventilation. Anaesthesia was maintained by sevoflurane in oxygen/air 1:1.

Monitoring consisted of pulse oximetry, ECG, end-tidal (E') gas analysis (sevoflurane, O_2, CO_2), and rectal temperature control. To prevent the pigs from moving, end-tidal sevoflurane 5 vol% (range 3.7–6.8) was needed. E'_{CO_2} (kPa) was held between 4.5 and 5. For application of the three different test solutions, the pigs were randomized into three groups of 15 individuals. Group 1 received bupivacaine 0.125%, Group 2 bupivacaine 0.125%+epinephrine 1:200 000, and Group 3 plain epinephrine 1:200 000. Under steady-state conditions 0.2 ml kg^{-1} and 10 min later 0.4 ml kg^{-1} of the selected test solution were administered i.v. followed by a rapid flush of 5 ml normal saline solution. One ECG lead (lead I, II, or III) was recorded electronically and continuously printed. The ECG lead was chosen according to best visibility of P-wave, QRS complex, and a positive T-wave. Later on an anaesthetist blinded to type of test dose analysed the ECG print out with particular regard to changes in heart rate and formation of T-wave elevation. An increase in heart rate of $\geq$10% above baseline, $\geq$25% of T-wave amplitude, or both was considered a positive response.

Randomization was decided by drawing lots. The Kruskal–Wallis non-parametric tests were performed to assess differences in the effects on heart rate changes between the groups followed by *post hoc* comparisons using the Bonferroni-corrected Mann–Whitney *U*-tests. The effects on T-wave elevation were analysed by Fisher's exact test. Computer package SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) was used. The level of significance was set at $P \leq 0.05$.

Results

The median weight of pigs and numbers of males and females were similar in all groups.

After injection of 0.2 ml kg^{-1} test solution, an increase in heart rate of $\geq$10% was found in 0% in Group 1 and in 100% in Groups 2 and 3 (both $P<0.001$). Similar results were observed after injection of 0.4 ml kg^{-1} test solution. In fact, in Group 1, there was a slight decrease in heart rate of -5.4% (median) after 0.2 ml kg^{-1} and of -7% after application of 0.4 ml kg^{-1} test solution.

T-elevation was present in 7% of the piglets in Group 1 and in 93% of the piglets in Groups 2 and 3 after application of 0.2 ml kg^{-1} test solution (both $P<0.001$). Injection of 0.4 ml kg^{-1} test solution caused T-elevation in 27%, 100%, and 100%, respectively (both $P<0.001$). In most cases, T-elevation started 15–20 s after injection of the test solution. In all positive cases, T-elevation occurred within 30 s. A typical ECG trace from each group is shown in Figure 1. Alterations caused by the different test solutions are listed in detail in Tables 1 and 2.

Discussion

This study investigated in an animal model whether i.v. applied epinephrine, bupivacaine, or their combination is

Table 1 ECG alterations after injection of 0.2 ml kg^{-1} test solution (n=45 piglets). Results are given in median and range. *$P<0.001$ between Groups 1 and 2; #$P<0.001$ between Groups 1 and 3

	Group 1	Group 2	Group 3
Test dose	Bupivacaine	Bupivacaine+epinephrine	Epinephrine
Change in heart rate (beats min^{-1})	−7 (−18 to 12)	89 (27–116)*	86 (73–127)#
Change in heart rate (% beats min^{-1})	−5.4 (−13 to 9)	74 (17–101)*	74 (42–123)#
T-elevation (yes/no)	1/14	14/1*	14/1#

Table 2 ECG alterations after injection of 0.4 ml kg^{-1} test solution (n=45 piglets). Results are given in median and range. *$P<0.001$ between Groups 1 and 2; #$P<0.001$ between Groups 1 and 3

	Group 1	Group 2	Group 3
Test dose	Bupivacaine	Bupivacaine+epinephrine	Epinephrine
Change in heart rate (beats min^{-1})	−8 (−16 to 0)	100 (60–132)*	102 (83–140)#
Change in heart rate (%beats min^{-1})	−7 (−13 to 0)	87 (42–112)*	78 (55–117)#
T-elevation (yes/no)	4/11	15/0*	15/0#

responsible for ECG alteration. The main findings were that tachycardia and elevation of T-wave amplitude after i.v. application of a commonly used LA test dose (0.2 ml kg^{-1}) are caused by epinephrine.

Although still debated, the administration of a test dose of LA is widely used in paediatric regional anaesthesia.[4] Test dose sensitivity varies according to the type of LA, the adjunct drug (epinephrine and isoproterenol), or both. Furthermore, the type of anaesthetic agents (halothane, isoflurane, and sevoflurane)[7] and whether atropine is administered before or not are also important.[4 8] We chose study conditions very close to routine clinical paediatric anaesthesia; no premedication with atropine, general anaesthesia with sevoflurane–oxygen–air, bupivacaine as LA, test dose of 0.2 ml kg^{-1} according to our institutional guidelines (1 μg kg^{-1} body weight epinephrine, maximum dose 15 μg per testing dose, which corresponds a recommended test dose for adults).[9–11]

Our results clearly demonstrate that the addition of epinephrine into the test dose has a sensitivity of 100% with regard to tachycardia and 93% with regard to T-elevation to detect intravascular administration of an LA test dose. Doubling the dose increased the sensitivity for T-elevation to 100%.

In the literature, several case series showed a high sensitivity of an epinephrine-containing test solution for heart rate elevation (positive if ≥10% increase in heart rate).[5 6 8 11–13] But in most of these reports, children were pretreated with atropine. This is in contrast to modern paediatric anaesthesia practice where atropine is not now routinely used as an adjunct to premedication, particularly since sevoflurane was introduced. Interestingly, atropine is known to enhance heart rate acceleration when epinephrine-containing test solutions are systemically applied.[8] Desparment and colleagues[8] found a sensitivity of as low as 76% without atropine pretreatment, whereas 95% of the patients showed a tachycardia under the same conditions (halothane, lidocaine+epinephrine) with 10 μg kg^{-1} atropine injected before the LA test dose. Another important issue is the fact that in most studies the epinephrine dose was 0.5 μg kg^{-1} compared with 1 μg kg^{-1} as used in our set-up. Although we rapidly applied 1 μg kg^{-1} epinephrine by the i.v. route, we never observed adverse side-effects such as ventricular or supraventricular arrhythmias. This is in accordance with other reports using epinephrine (usually 0.5 μg kg^{-1}).[6 14–16]

Elevation of T-wave amplitude caused by an inadvertent intravascular injection of an epinephrine-containing LA test dose was first described by Freid and colleagues.[17] The mechanisms responsible for these ECG changes were not previously known. T-wave changes have been found when only epinephrine,[7] LA,[18] or both agents together was administered.[5 6 11 19] In these studies epinephrine and LA+epinephrine caused T-elevations, even with very small doses as, for example, test doses. In a report where T-elevation was caused by the LA, the full dose for a caudal block was i.v. applied in a 2-month-old infant.[18] In our study, T-elevation caused by a bupivacaine standard test dose (0.2 ml kg^{-1}) occurred in only 7% of the animals and increased to 27% with the higher test dose (0.4 ml kg^{-1}) applied. Therefore, we suggest that bupivacaine alone can produce T-elevation, but higher and potentially toxic doses are required. Under these conditions, bupivacaine without adjunct cannot serve as a reliable test dose.

The selection of ECG lead during administration of an epinephrine-containing test dose is not important, as shown by Ogasawara and colleauges.[16] They demonstrated that there was no significant difference in transient changes in T-wave amplitude in ECG leads I, II, III, or V_5.[16] These leads were equally effective for detecting intravascular injection of an epinephrine-containing test dose in sevoflurane-anaesthetized children.

It is known that an epinephrine-containing test dose may increase arterial pressure.[4] Unfortunately, in our small pigs, it was very difficult to obtain reliable arterial pressure values in a non-invasive manner.

Although we have chosen the study conditions as close to modern paediatric anaesthesia practice as possible and

the pig model is the closest to humans, our results do not fully reflect similar responses in children. In particular, we used newborn pigs. In humans, it was demonstrated that T-wave elevation is age-dependent. In children aged 6–72 months, a significant negative linear correlation was found between age and the maximal per cent increase in T-wave amplitude.[5] In adults, i.v. epinephrine caused flattening or inversion of the T-wave.[14 15] Thus, further clinical studies in children are needed.

On the basis of our study results, an epinephrine-containing LA solution and ECG control should be used for the reliable detection of inadvertent intravascular LA injection in children. Since a cannula placed in the epidural (caudal), axillar, or other spaces easily can dislodge into a vessel, particularly when a syringe is changed, epinephrine should be used for the full dose. Whether epinephrine should be used only for the test dose or for the full dose is a controversial issue.

In conclusion, this newborn animal model demonstrates that T-elevation in the ECG during i.v. application of a common test dose of bupivacaine is caused by epinephrine addition. Whether these epinephrine responses are age-dependent in children and whether higher doses of bupivacaine alone can cause similar ECG changes or not requires further studies.

Funding

The donation was made by UBS AG by order of a client and by 'Stiftung für wissenschaftliche Forschung' at the University of Zurich, Switzerland.

References

1 Polaner DM, Suresh S, Coté CJ. Regional anesthesia. In: Coté CJ, Lerman J, Todres ID, eds. *A Practice of Anesthesia for Infants and Children*. Philadelphia: Saunders Elsevier, 2009; 867

2 Timmerman L, Megens J. Detecting intravascular injection during caudal anaesthesia in children. *Eur J Anaesthesiol* 2007; **24**: 1057–69

3 Fisher QA, Shaffner DH, Yaster M. Detection of intravascular injection of regional anaesthetics in children. *Can J Anaesth* 1997; **44**: 592–8

4 Tobias JD. Caudal epidural block: a review of test dosing and recognition of systemic injection in children. *Anesth Analg* 2001; **93**: 1156–61

5 Tanaka M, Nishikawa T. Evaluating T-wave amplitude as guide for detecting intravascular injection of a test dose in anesthetized children. *Anesth Analg* 1999; **88**: 754–8

6 Tanaka M, Nishikawa T. The efficacy of a simulated intravascular test dose in sevoflurane-anesthetized children: a dose–response study. *Anesth Analg* 1999; **89**: 632–7

7 Kozek-Langenecker SA, Marhofer P, Jonas K, Macik T, Urak G, Semsroth M. Cardiovascular criteria for epidural test dosing in sevoflurane- and halothane-anesthetized children. *Anesth Analg* 2000; **90**: 579–83

8 Desparment J, Mateo J, Ecoffey C, Mazoit X. Efficacy of an epidural test dose in children anesthetized with halothane. *Anesthesiology* 1990; **72**: 249–51

9 Moore DC, Batra MS. The components of an effective test dose prior to epidural block. *Anesthesiology* 1981; **55**: 693–6

10 Guinard JP, Mulroy MF, Carpenter RL, Knopes KD. Test doses: optimal epinephrine content with and without acute beta-adrenergic blockade. *Anesthesiology* 1990; **73**: 386–92

11 Tanaka M, Kimura T, Goyagi T, Ogasawara K, Nitta R, Nishikawa T. Evaluating hemodynamic and T wave criteria of simulated intravascular test doses using bupivacaine or isoproterenol in anesthetized children. *Anesth Analg* 2000; **91**: 567–72

12 Tanaka M, Nishikawa T. Simulation of an epidural test dose with epinephrine content with and without acute beta-adrenergic blockade. *Anesth Analg* 1998; **86**: 952–7

13 Sethna NF, Sullivan L, Retik A, *et al*. Efficacy of simulated epinephrine-containing epidural test dose after intravenous atropine during isoflurane anesthesia in children. *Reg Anesth Pain Med* 2000; **25**: 566–72

14 Tanaka M, Goyagi T, Kimura T, Nishikawa T. The efficacy of hemodynamic and T wave criteria for detecting intravascular injection of epinephrine test doses in anesthetized adults: a dose–response study. *Anesth Analg* 2000; **91**: 1196–202

15 Tanaka M, Nishikawa T. A comparative study of hemodynamic and T-wave criteria for detecting intravascular injection of the test dose (epinephrine) in sevoflurane-anesthetized adults. *Anesth Analg* 1999; **89**: 32–6

16 Ogasawara K, Tanaka M, Nishikawa T. Choice of electrocardiography lead does not affect the usefulness of the T-wave criterion for detecting intravascular injection of an epinephrine test dose in anesthetized children. *Anesth Analg* 2003; **97**: 372–6

17 Freid EB, Bailey AG, Valley RD. Electrocardiographic and hemodynamic changes associated with unintentional intravascular injection of bupivacaine with epinephrine in infants. *Anesthesiology* 1993; **79**: 394–8

18 Tanaka M, Nitta R, Nishikawa T. Increased T-wave amplitude after accidental intravascular injection of lidocaine plus bupivacaine without epinephrine in sevoflurane-anesthetized child. *Anesth Analg* 2001; **92**: 915–7

19 Sparks JW, Seefelder C. Neonatal T-wave elevation from a positive epidural test dose. *Paediatr Anaesth* 2005; **15**: 706–7